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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/920,033	08/01/2001	Rosanne M. Crooke	ISPH-0592	5785

7590 01/14/2003

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EXAMINER	
EPPS, JANET L	

ART UNIT	PAPER NUMBER
1635	9

DATE MAILED: 01/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/920,033	CROOKE ET AL.	
	Examiner	Art Unit	
	Janet L Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication app ars on the cov r sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-20* is/are pending in the application.

4a) Of the above claim(s) *15-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-14 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-14 and 20 and SEQ ID NO: 3, with traverse in Paper No. #8 is acknowledged. The traversal is on the ground(s) that all of the claims target a specific gene, namely apolipoprotein B, each of the claims contain the components for the use in the same endpoint, and finally that a search relating to apolipoprotein B would identify art related to every claim in this application, and would not be overly burdensome to the examiner. This is not found persuasive because contrary to Applicant's assertions, as per MPEP § 803, "For purposes of the initial requirement, a serious burden on the examiner may be *prima facie* shown if the examiner shows by appropriate explanation of separate classification, or separate status in the art, or a different field of search as defined in MPEP § 808.02." As stated in the initial restriction requirement, the claims of group I are classified in 536, 24.5, and the claims of group II are classified in 435, 375.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-2, 4-14, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tang et al. in view of Branch and Monia et al.

Claims 1-2, 4-14, and 20 recite (1) a compound 8 to 50 nucleotides in length targeted to a nucleic acid molecule encoding apolipoprotein B (SEQ ID NO: 3), wherein said compound specifically hybridizes with and inhibits the expression of a nucleic acid molecule encoding apolipoprotein B; (2) the compound of claim 1 which is an antisense oligonucleotide; (4-10) The compound of claim 2 wherein the antisense oligonucleotide comprises a modified internucleoside linkage, a phosphorothioate linkage, wherein the antisense comprises a modified sugar moiety, a modified nucleobase, and wherein the antisense is a chimeric oligonucleotide; (11) A compound 8 to 50 nucleotides in length (12) A composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier or diluent; (13) wherein the composition of claim 12 comprises a colloidal dispersion system; (14) the composition of claim 12 wherein the compound is an antisense oligonucleotide.

Tang et al. describe the use of antisense oligodeoxynucleotides to reduce the level of apoplipoprotein expression in cultured liver cells in order to understand its mechanism of action. The method of Tang et al. comprises treating cultured liver cells with synthesized Apo B gene antisense in a 0.9% salt solution and measuring the Apo B100 concentration by RT-PCR. Tang et al. concluded that the ApoB gene antisense oligodeoxynucleotide inhibited Apo B gene expression and reduced Apo B concentration (see English abstract provided).

However, Tang et al. does not teach wherein the antisense oligodeoxynucleotide is 8 to 50 nucleotides in length, and modified, or wherein the composition comprises a colloidal dispersion system.

Branch teach that in order to maximize target site specificity the length of antisense oligonucleotides should be 17 base pairs or longer, since sequences of 17 base pairs or more would have a high probability of occurring only once in the haploid human genome (p. 47, para. 5-6). It is noted that the limitation "8 to 50 nucleotides in length" encompasses wherein the oligonucleotide is about 17 base pairs in length.

Monia et al. describe methods for the modulation of expression of the human ras oncogene in a cell comprising the administration of modified antisense oligonucleotides. The oligonucleotides used in the methods of Monia et al. are preferably chimeric oligonucleotides that contain two or more chemically distinct regions, each made up of at least one nucleotide. These oligonucleotides typically contain at least one region of modified nucleotides that confers one or more beneficial properties (such as, for example, increased nuclease resistance, increased uptake into cells, increased binding affinity for the RNA target) and a region that is a substrate for enzymes capable of cleaving RNA: DNA or RNA: RNA hybrids (col. 6, lines 49-67). The modified antisense oligonucleotides used in the *in vitro* inhibition methods of Monia et al. may comprise phosphorothioate internucleoside modifications, a 5-methylcytosine modifed nucleobase, and may further comprise 2'-methoxyethoxy sugar modifications (col. 7-8). The antisense oligonucleotide modifications disclosed by Monia et al. have been shown to increase both binding affinity of the oligonucleotide for its target and nuclease resistance of the oligonucleotide (col. 6, lines 45-58). Furthermore, Monia et al. teach the use of pharmaceutical carriers to facilitate the uptake of oligonucleotides into cells. These carriers include: ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Compositions for oral administration include powders or granules, suspensions

or solutions in water or non-aqueous media, capsules, sachets, or tablets. Thickeners, flavorings, diluents, emulsifiers, dispersing aids or binders may be desirable. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Coated condoms, gloves and the like may also be useful, cationic lipids may be included in the formulation to facilitate oligonucleotide uptake (col. 7, lines 40-67).

It would have been obvious to one of ordinary skill in the art to modify the teachings of Tang et al. to design antisense oligonucleotides of about 17 nucleobases in length (Branch), modifying those antisense oligonucleotides with phosphorothioate linkages, 2'-methoxyethoxy modified sugar residues, and a 5'-methylcytosine modified nucleobase (Monia et al.), in order to maximize target site specificity (Branch), and increase hybridization efficiency as well as maintaining nuclease resistance of said antisense oligonucleotide (Monia et al.).

Furthermore, it would have been obvious to one of ordinary skill in the art at the time of filing of the instant application to modify the teaching of Tang et al. with the teachings of Monia et al. since Tang et al. provide explicit disclosure and motivation for designing antisense targeting Apo B mRNA. One of ordinary skill in the art would have been motivated to design antisense oligonucleotides of about 17 nucleotides in length targeting Apo B and comprising the modifications taught by Monia et al. since modified oligonucleotides according to the preferred embodiments of Monia et al. possess a high target site specificity and increased cellular uptake in comparison to unmodified antisense oligonucleotides.

Therefore, the invention as a whole would have been *prima facie* obvious over Tang et al. in view of Branch and Monia et al.

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on M-T, Thurs-Friday 9:00AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703)-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-746-5143 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE
January 13, 2003

SEAN McGARRY
PRIMARY EXAMINER